Efficacy of Continuous Subcutaneous Insulin Infusion in Elderly Patients with Type 2 Diabetes Mellitus: A Meta-Analysis and Trial Sequential Analysis (Post-Print)

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Abstract

Background Insulin plays a crucial role in the management of diabetes mellitus. It can be administered through multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) via insulin pumps. Currently, controversy remains regarding the comparative effectiveness of these two delivery methods in elderly patients with type 2 diabetes mellitus (T2DM).

Objective To evaluate the therapeutic efficacy of CSII in elderly T2DM patients using Meta-analysis, and to employ trial sequential analysis (TSA) to assess the validity of the Meta-analysis findings.

Methods Electronic database searches were conducted for randomized controlled trials (RCTs) investigating CSII in elderly T2DM patients, published from inception to December 31, 2021, across The Cochrane Library, PubMed, Embase, Medline, Scopus, Web of Science, CNKI, Wanfang, VIP, and Chinese Biomedical Literature Database. Two investigators independently performed literature screening, quality assessment, and data extraction. Meta-analysis of eligible studies meeting quality criteria was conducted using Review Manager 5.3 software, and trial sequential analysis was performed using TSA v0.9 developed by the Copenhagen Trial Unit.

Results Sixteen RCTs were included. Meta-analysis results demonstrated that the experimental group exhibited superior outcomes compared with the control group in improving fasting plasma glucose (FPG) [MD=-0.82, 95%CI (-1.09, -0.54), P<0.05], 2-hour postprandial glucose (2hPG) [MD=-0.76, 95%CI (-1.39, -0.14), P<0.05], glycated hemoglobin (HbA1c) [SMD=-1.23, 95%CI (-2.23, -0.23), P<0.05], incidence of severe hypoglycemia [RD=-0.10, 95%CI (-0.17, -0.03), P<0.05], daily insulin dosage [MD=-9.63, 95%CI (-12.35, -6.92), P<0.05], and mean amplitude of glycemic excursions (MAGE) [MD=-1.19, 95%CI (-1.40,

-0.97), P<0.05]. Trial sequential analysis of primary outcome measures yielded consistent affirmative conclusions, confirming that CSII treatment significantly reduces FPG, 2hPG, HbA1c levels, and the incidence of severe hypoglycemia in elderly T2DM patients.

Conclusion Compared with MDI, CSII can further improve glycemic control, reduce the incidence of hypoglycemia and glycemic variability, while also offering certain economic benefits in elderly T2DM patients. This study has been registered with PROSPERO (registration number: CRD42021283729).

Full Text

Meta-Analysis and Trial Sequential Analysis of the Effect of Continuous Subcutaneous Insulin Infusion in the Treatment of Elderly Adults with Type 2 Diabetes Mellitus

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Abstract

Background: Insulin plays an important role in the treatment of diabetes and can be administered either by multiple daily injections (MDI) or by continuous subcutaneous insulin infusion (CSII) via insulin pump. There is still controversy about the effectiveness of both injection methods among elderly adults with type 2 diabetes mellitus (T2DM). **Objective:** Meta-analysis was used to evaluate the effectiveness of CSII among elderly adults with T2DM, and the validity of the results was tested using trial sequential analysis (TSA). **Methods:** The Cochrane Library, PubMed, Embase, Medline, Scoups, Web of Science, CNKI, Wanfang Database, CQVIP, and CBM were systematically searched for randomized controlled trials (RCTs) published from inception to December 31, 2021, regarding the application of CSII among elderly adults with T2DM. Two researchers independently screened the retrieved literature, evaluated quality, and extracted data. Meta-analysis of literature meeting quality standards was performed using Review Manager 5.3 software, and trial sequential analysis was completed using TSA v0.9, developed by the Copenhagen Clinical Trial Centre. **Results:** A total of 16 RCTs were included. The experimental group outperformed the control group in improving fasting plasma glucose (FPG) [MD=-0.82, 95%CI(-1.09, -0.54), P<0.05], 2-hour postprandial blood glucose (2hPG) [MD=-0.76, 95%CI(-1.39, -0.14), P<0.05], glycosylated hemoglobin (HbA1c) [SMD=-1.23, 95%CI(-2.23, -0.23), P<0.05], incidence of severe hypoglycemia [RD=-0.10, 95%CI(-0.17, -0.03), P<0.05], daily insulin dose [MD=-9.63, 95%CI(-12.35, -6.92), P<0.05], and mean amplitude of glycemic excursions (MAGE) [MD=-1.19, 95%CI(-1.40,

-0.97), P<0.05]. Trial sequential analysis of the main outcome indicators likewise led to the same conclusion that CSII treatment significantly reduced FPG, 2hPG, HbA1c levels and the incidence of severe hypoglycemia among elderly adults with T2DM. **Conclusion:** Compared to MDI, CSII can further improve glycemic control, reduce the incidence of hypoglycemia and the magnitude of glycemic fluctuations among elderly patients with T2DM, and also has some economic benefits. This study has been registered on PROSPERO under registration number CRD42021283729.

Keywords: insulin; elderly adults; type 2 diabetes mellitus; blood glucose; meta-analysis

Introduction

Diabetes is a chronic metabolic disease characterized by hyperglycemia resulting from insulin secretion defects. Its prevalence is notably high among elderly populations, with approximately 95% of cases being type 2 diabetes mellitus (T2DM) [1][2]. Global data indicate that elderly T2DM patients account for about 50% of the total diabetic population [2]. With advancing age and disease progression, elderly T2DM patients experience gradual deterioration of pancreatic β-cell function accompanied by varying degrees of insulin resistance [4], often exhibiting large glycemic fluctuations, multiple chronic complications, and suboptimal glycemic control [5]. Early insulin therapy is recommended for hyperglycemia that cannot be alleviated by oral hypoglycemic agents and dietary management [5]. Currently, the commonly used insulin injection methods are multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII) via insulin pump. Insulin pumps are intelligent controlled devices that enable relatively precise continuous insulin infusion, simulating physiological insulin secretion [7]. While declines in cognitive ability, finger dexterity, and vision may limit insulin pump use among elderly patients [8], the continuous refinement and convenience of insulin pumps have gradually expanded their application in elderly diabetic populations [9]. Clinically, CSII is increasingly used to improve glycemic control and enhance insulin safety in elderly T2DM patients. However, controversy remains regarding the therapeutic effects of the two insulin injection methods, and relevant guidelines suggest that only small-sample studies indicate insulin pumps may be more effective in controlling blood glucose [10]. Therefore, this study employs meta-analysis to synthesize multiple small-sample studies, comparing and evaluating the therapeutic effects of CSII and MDI in elderly T2DM patients to provide reliable evidence for clinical practice.

Methods

This study has been registered on the international systematic review registration platform PROSPERO (registration number: CRD42021283729).

1.1 Literature Search Strategy

We systematically searched The Cochrane Library, PubMed, Embase, Medline, Scoups, Web of Science, CNKI, Wanfang Database, CQVIP, and CBM for RCTs on CSII therapy in elderly T2DM patients from database inception to December 2021. Search terms were imported into CQVIP' s "synonym" search to identify similar terms, and correct expressions were obtained by consulting the English MeSH vocabulary and Chinese Medical Subject Headings (CMeSH). We then searched databases using a combination of subject terms and free terms, supplemented by snowball searching of references from retrieved literature. The search strategy for Cochrane Library is detailed in Table 1 .

1.2.1 Inclusion Criteria

(1) **Study type:** Published randomized controlled trials (RCTs) in Chinese or English. (2) **Study subjects:** Diagnosed with diabetes according to 1999 WHO criteria: fasting plasma glucose $ $7.0 mmol/L, or 2-hour post-OGTT glucose $ $11.1 mmol/L, or random glucose $ $11.1 mmol/L with typical diabetes symptoms [11]; Type 2 diabetes; Age $ $60 years [12]; Non-perioperative patients; No severe pulmonary, hepatic, or renal insufficiency; No other severe cardiovascular or cerebrovascular diseases; No psychiatric disorders; No malignant tumors; No recent diabetic ketoacidosis or hyperosmolar coma. (3) **Interventions:** The experimental group received CSII therapy via insulin pump, while the control group received MDI therapy. (4) **Outcome measures:** Primary outcomes: fasting plasma glucose (FPG), 2-hour postprandial plasma glucose (2hPG), glycosylated hemoglobin (HbA1c), and hypoglycemia incidence; Secondary outcomes: mean amplitude of glycemic excursion (MAGE), daily insulin dose, and time to glycemic target.

1.3 Literature Screening and Data Extraction

Two researchers independently conducted literature screening and data extraction. Search results from the ten databases were imported into EndNote X9. After removing duplicates, the two researchers screened titles and abstracts according to inclusion criteria, reading full texts when necessary to identify eligible studies. The initially selected literature from both researchers was compared, with identical studies included and disputed studies resolved through discussion or consultation with a third researcher. Extracted data included basic information (first author and year), country, sample size, patient age, intervention methods for experimental and control groups, intervention duration, and outcome measures.

1.4 Literature Quality Assessment

The Cochrane risk of bias assessment tool recommended in the Cochrane Handbook version 6.2 [13] was used to evaluate the methodological quality of included

studies. This tool comprises seven items: random sequence generation, allocation concealment, performance bias, detection bias, attrition bias, reporting bias, and other bias. Each item was rated as "low risk,""high risk,"or "unclear."Considering the difficulty of blinding participants and researchers to insulin injection methods, studies without explicit description of participant blinding were classified as high risk for performance bias. Two researchers independently assessed methodological quality, compared results, discussed disputed items, and invited a third researcher to arbitrate when consensus could not be reached.

1.5 Statistical Methods

(1) **Assessment of reporting bias:** Funnel plots were used to assess potential publication bias. (2) **Treatment effect analysis:** RevMan 5.3 software was used for meta-analysis. For dichotomous data, risk difference (RD) with 95% confidence interval (CI) was used as the effect measure. For continuous data, mean difference (MD) was used when the same measurement tool was employed; otherwise, standardized mean difference (SMD) with 95% CI was calculated. (3) **Heterogeneity assessment:** The X^2 test was used to determine heterogeneity among studies. If I^2<50% and P>0.1, a fixed-effects model was used; if $I^2$$ 50 $0.1, indicating heterogeneity, subgroup analysis was performed when clinical heterogeneity sources could be identified after discussion. When heterogeneity sources could not be identified, a random-effects model or descriptive analysis was selected. (4) **Sensitivity analysis:** A leave-one-out approach was used to evaluate the stability of meta-analysis results. (5) **Trial sequential analysis (TSA):** TSA v0.9 software developed by the Copenhagen Clinical Trial Centre was used, with type I error probability set at 0.05 and test power at 0.80. For dichotomous outcomes, relative risk reduction and control group event rate were used as effect values; for continuous outcomes, mean difference and variance were used as effect values to automatically generate the required information size (RIS). The traditional boundary Z=1.96 was set, and TSA was performed on primary outcomes with significant differences to determine the impact of random error on meta-analysis results.

Results

2.1 Included Literature

A total of 2,028 articles were identified. After duplicate removal and abstract screening using EndNote X9, 78 articles were obtained. After full-text reading and applying inclusion and exclusion criteria, 62 articles of low quality or not meeting requirements were excluded, leaving 16 RCTs [14-29]. The literature screening process is shown in Figure 1 [Figure 1: see original paper]. Basic characteristics of included studies are presented in Table 2 .

2.2 Risk of Bias Assessment

Among the included studies, six [19] described the random allocation method, while others mentioned randomization without specifying the method (Table 3).

2.3.1 Fasting Plasma Glucose (FPG)

Eleven studies [15-16,18-22,25,27-29] using FPG as an outcome were included. Heterogeneity test: I^2=43%, P=0.06. After comprehensive consideration of I^2 and P values, a random-effects model was used. Results showed that CSII group had lower FPG levels than MDI group after treatment, with statistically significant difference [MD=-0.82, 95%CI(-1.09, -0.54), P<0.05] (Figure 2 [Figure 2: see original paper]).

2.3.2 2-Hour Postprandial Glucose (2hPG)

Eleven studies [15-16,18-22,25,27-29] using 2hPG as an outcome were included. Heterogeneity test: I^2=87%, P<0.1, indicating high heterogeneity. After excluding clinical heterogeneity, a random-effects model was used. Results showed that CSII group had lower 2hPG levels than MDI group after treatment, with statistically significant difference [MD=-0.76, 95%CI(-1.39, -0.14), P<0.05] (Figure 3 [Figure 3: see original paper]).

2.3.3 Glycosylated Hemoglobin (HbA1c)

Six studies [14-17,19-20] using HbA1c as an outcome were included. Heterogeneity test: I^2=94%, P<0.1, indicating high heterogeneity. After clinical heterogeneity discussion, subgroup analysis was performed by dividing studies into two groups: intervention duration $ $1 month and >1 month. After excluding clinical heterogeneity, a random-effects model was used. Results showed that CSII group was superior to MDI group in improving HbA1c levels, with statistically significant difference [SMD=-1.23, 95%CI(-2.23, -0.23), P<0.05] (Figure 4 [Figure 4: see original paper]).

2.3.4 Hypoglycemia Incidence

Five studies [14-15,18-19,28] using hypoglycemia incidence as an outcome were included. Based on different degrees of hypoglycemia reported, studies were divided into two subgroups: non-severe hypoglycemia (blood glucose $ $3.9 mmol/L) and severe hypoglycemia (blood glucose $ $2.8 mmol/L). Two studies [14,19] reported both non-severe and severe hypoglycemia incidence. Since Fu et al. [19] reported no severe hypoglycemia in either group, a fixed-effects model was used with RD as the effect measure. Results showed no statistically significant difference in non-severe hypoglycemia incidence between the two methods [RD=-0.04, 95%CI(-0.12, 0.04), P=0.29], but a statistically significant difference

in severe hypoglycemia incidence [RD=-0.10, 95%CI(-0.17, -0.03), P<0.05], suggesting better safety of CSII in elderly T2DM patients (Figure 5 [Figure 5: see original paper]).

2.3.5 Daily Insulin Dose

Six studies [17-19,21,27-28] using daily insulin dose as an outcome were included. Heterogeneity test: I^2=69%, P=0.007, indicating high heterogeneity. After excluding clinical heterogeneity, a random-effects model was used. Results showed that CSII group had lower daily insulin dose than MDI group, with statistically significant difference [MD=-9.63, 95%CI(-12.35, -6.92), P<0.05] (Figure 6 [Figure 6: see original paper]).

2.3.6 Mean Amplitude of Glycemic Excursion (MAGE)

Three studies [23-24,26] using MAGE as an outcome were included. Heterogeneity test: I^2=0%, P=0.69. A fixed-effects model was used. Results showed that CSII group had lower MAGE levels than MDI group, with statistically significant difference [MD=-1.19, 95%CI(-1.40, -0.97), P<0.05], indicating that CSII can effectively reduce glycemic fluctuations in elderly T2DM patients compared to MDI (Figure 7 [Figure 7: see original paper]).

2.3.7 Time to Glycemic Target

Six studies [15-17,19,21,28] using time to glycemic target as an outcome were included. Heterogeneity test: I^2=84%, P<0.1, indicating high heterogeneity. Due to different glycemic control standards across studies, we categorized them into three types. Combined meta-analysis results showed that CSII group achieved glycemic targets faster under different control standards (Table 4).

2.4 Sensitivity Analysis

The forest plot for 2hPG showed that one study [27] was clearly outside the overall trend. After removing this study, the combined result showed no significant change, indicating good stability of included studies. The forest plot for HbA1c showed that Xie et al. [16] was clearly outside the overall trend. After removing this study and repeating meta-analysis, the difference in HbA1c between groups was no longer statistically significant [SMD=-0.49, 95%CI(-1.23, 0.24), P=0.19], indicating poor stability for this outcome.

2.5.1 Comparison of FPG Between Groups

TSA results for FPG comparison are shown in Figure 8 [Figure 8: see original paper]. The cumulative Z curve crossed both the traditional boundary and TSA boundary before Li et al. [20], allowing early confirmation that CSII treatment significantly improved FPG levels in elderly T2DM patients. Subsequent

studies also reached the required information size (RIS), further confirming the conclusion.

2.5.2 Comparison of 2hPG Between Groups

TSA results for 2hPG comparison are shown in Figure 9 [Figure 9: see original paper]. After including 11 studies, the cumulative Z curve crossed the TSA boundary. Although the cumulative information size did not reach the expected value, no more trials were needed, and early confirmation could be obtained that CSII treatment significantly improved 2hPG levels in elderly T2DM patients.

2.5.3 Comparison of HbA1c Between Groups

TSA results for HbA1c comparison are shown in Figure 10 [Figure 10: see original paper]. After Pei et al. [15], the cumulative Z curve crossed both the traditional boundary and TSA boundary, allowing early confirmation that CSII was superior to MDI in improving HbA1c.

2.5.4 Comparison of Severe Hypoglycemia Incidence Between Groups

TSA results are shown in Figure 11 [Figure 11: see original paper]. After including three studies, the cumulative Z curve crossed the traditional boundary but not the TSA boundary, and the cumulative information size did not reach RIS, suggesting that traditional meta-analysis may have yielded false-positive conclusions. More trials are needed in the future to confirm the safety difference between the two injection methods.

2.6 Reporting Bias Analysis

Funnel plot analysis of the 16 included studies showed that funnel plots for FPG and 2hPG were not completely symmetrical, suggesting possible publication bias (Figures 12-13 [Figure 12: see original paper][Figure 13: see original paper]).

Discussion

3.1 Glycemic Control Effects of CSII in Elderly T2DM Patients

With increasing age and disease duration, elderly T2DM patients experience gradual decline in pancreatic β-cell function, with reduced insulin secretion and reserve capacity [30], leading to elevated immediate blood glucose including FPG and especially 2hPG [5]. Combined with decreased self-management ability, long-term glycemic control is often unsatisfactory [10]. Although MDI is commonly used clinically, each large-dose insulin injection can accumulate and form "insulin depots," causing local subcutaneous tissue hyperplasia and affecting insulin absorption [31]. While Herman et al. [14] found no statistically significant difference in glycemic control between CSII and MDI ($P>0.05$), our meta-analysis showed that CSII was superior to MDI in controlling both immediate glucose (FPG and 2hPG) and long-term glucose levels (HbA1c), with TSA

confirming these conclusions. This may be because CSII continuously infuses insulin in small doses, reducing subcutaneous insulin accumulation and enabling more complete absorption. It may also be related to avoiding needle leakage or skin leakage from improper injection technique [32], making insulin dosing more precise. Therefore, CSII is recommended for glycemic control in elderly T2DM patients.

3.2 Treatment Safety of CSII in Elderly T2DM Patients

Hypoglycemia is a potential complication of insulin therapy. Elderly patients have higher hypoglycemia risk than non-elderly patients due to factors including age, impaired glucose regulation, reduced hepatic and renal function, and polypharmacy [33][34]. Hypoglycemia is an important cause of short-term and long-term adverse clinical outcomes and increased mortality in elderly T2DM patients [10]. Therefore, preventing hypoglycemia and improving insulin therapy safety are urgent issues in diabetes management. Our results showed no statistically significant difference in non-severe hypoglycemia (blood glucose $ $3.9 mmol/L) incidence between CSII and MDI ($P>0.05$), but CSII had significantly fewer severe hypoglycemia (blood glucose $ $2.8 mmol/L) cases than MDI ($P<0.05$). Karges et al. [35] similarly found that CSII reduced severe hypoglycemia risk compared to MDI. This may be related to insulin pump delivery patterns. Insulin pumps can continuously and precisely infuse insulin in small doses according to different physiological activities and multi-meal requirements, maximizing physiological insulin secretion simulation. Additionally, some CSII systems integrated with hypoglycemia alarms can improve hypoglycemia detection efficiency, and insulin infusion suspension based on low glucose values can greatly reduce hypoglycemia events and prevent progression to severe hypoglycemia [36]. However, TSA showed that the cumulative Z curve did not cross the TSA boundary, suggesting possible false-positive results and insufficient sample size. No definitive conclusion can be drawn, and more studies are needed to clarify safety differences.

3.3 Glycemic Stability Effects of CSII in Elderly T2DM Patients

Glycemic variability refers to unstable fluctuations in blood glucose between peaks and troughs [38]. Elderly patients with impaired glucose regulation, polypharmacy, and poor treatment compliance are more prone to glycemic fluctuations and represent a key population [39]. Glycemic variability is closely related to the development of diabetes chronic complications [40], with potentially greater harm than persistent hyperglycemia [41]. Our meta-analysis showed that CSII-treated patients had significantly lower MAGE than MDI-treated patients, indicating better glycemic stability. This may be because CSII can flexibly allocate pre-meal insulin doses and basal infusion rates, with continuous micro-infusion effectively reducing dawn phenomenon and postprandial hyperglycemia [42], thereby decreasing glycemic fluctuation amplitude. Glycemic variability control is receiving increasing attention, with evaluation indicators

such as time in range (TIR) and coefficient of variation (CV) becoming internationally recognized [5]. However, research on these indicators remains limited, especially in elderly T2DM populations. Future studies should explore CSII effects on other evaluation indicators to more comprehensively assess its role in controlling glycemic variability.

3.4 Economic Analysis of CSII in Elderly T2DM Patients

Our meta-analysis showed that CSII therapy effectively reduced daily insulin dose and achieved glycemic targets faster, thereby shortening hospitalization time. Some studies have found that CSII can improve and delay diabetes chronic complications such as peripheral neuropathy and diabetic nephropathy compared to MDI [43], demonstrating certain economic benefits. Although insulin pumps are convenient, stable, and precise, eliminating the pain of multiple daily injections, they are expensive (even domestic pumps cost over 10,000 RMB) and are not covered by medical insurance in many countries, increasing patient financial burden. Cost-effectiveness analysis [45] found that MDI was more economical than CSII, but CSII showed better incremental cost-effectiveness, meaning the additional cost per unit of effectiveness increase was lower for CSII than MDI. This may be because CSII reduces diabetes complication risk, partially offsetting its higher acquisition cost through reduced complications [46].

3.5 Heterogeneity Analysis

Except for FPG and MAGE, meta-analysis results for other outcomes showed substantial heterogeneity. Possible reasons include: First, elderly patients have significant clinical heterogeneity [10]. For example, baseline HbA1c levels were around 8.2% in Herman et al. [14] but 11.62% in Lang et al. [28], indicating heterogeneous baseline glycemic control. Second, intervention durations varied substantially, from 12 months in Herman et al. [14] to only 1 week in Xu et al. [22].

3.6 Strengths and Limitations

CSII usage in elderly T2DM patients has increased in recent years, with related trials continuously emerging. However, controversy remains about treatment effects of CSII versus MDI in this population, without definitive evidence. This study provides evidence from four therapeutic effect dimensions, synthesizing various indicators to inform clinical practice and address relevant controversies. However, limitations exist: (1) High clinical heterogeneity and possible publication bias may affect result reliability; (2) Some outcomes like severe hypoglycemia incidence and MAGE had few included studies, affecting argument strength and suggesting the need for more CSII application studies focusing on hypoglycemia incidence and glycemic variability.

Author Contributions

CHENG Kangyao, WANG Yin, and YANG Bei conceived and designed the study, analyzed and interpreted results. YANG Bei and HAN Lin collected and organized data. YANG Bei, HAN Lin, and CHENG Kangyao performed statistical analysis. YANG Bei drafted the manuscript. CHENG Kangyao revised the manuscript. WANG Yin was responsible for quality control and review. CHENG Kangyao and WANG Yin had overall responsibility and supervised the study.

Conflicts of Interest: None declared.

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